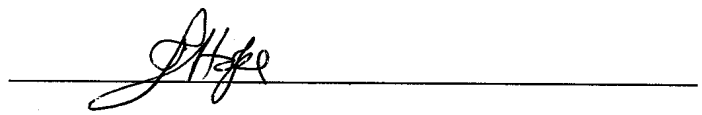
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION

I, Janet Hope, BSc(Hons.), MIL., MITI., translator to Taylor and Meyer of 20 Kingsmead Road, London SW2 3JD, England, do solemnly and sincerely declare as follows:

1. That I am well acquainted with the English and German languages;
2. That the following is a true translation made by me into the English language of German Priority Text Application No. 101 46 275.1
3. That all statements made herein of my own knowledge are true and
   that all statements made on information and belief are believed to be true;
   and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

Signed, this 4th day of February 2008,



Stoke Goldington, Bucks., MK16 8QN, England

FEDERAL REPUBLIC OF GERMANY

Certificate of Priority for Filing of a Patent Application

Filing number:	101 46 275.1
Filing date:	18th September 2001
Applicant/Proprietor:	Grünenthal GmbH, Aachen/Germany;
Title:	Combination of selected opioids with muscarine antagonists for treating urinary incontinence
IPC:	A 61 K 31/485

The attached papers are a true and accurate reproduction of the original documents of this patent application.

Munich, 19th August 2002
On behalf of the President of the German Patent and Trade Mark Office

(signature)

Wehner

Patent Application of Grünenthal GmbH, D-52078 Aachen
(applicant's reference: G 3084)

Combination of selected opioids with muscarine antagonists for treating urinary incontinence

The invention relates to the use of a combination of compounds of group A, in particular opioids, and compounds of group B, in particular anti-muscarine agents and other substances which have a predominantly peripheral action, for the preparation of a medicament for treatment of an increased urge to urinate or urinary incontinence and to corresponding medicaments and methods for treatment of an increased urge to urinate or urinary incontinence.

Urinary incontinence is the involuntary discharge of urine. This occurs in an uncontrolled manner when the pressure within the urinary bladder exceeds the pressure needed to close the ureter. Causes can be on the one hand an increased internal pressure in the bladder (e.g. due to detrusor instability) with the consequence of urgency incontinence, and on the other a reduced sphincter pressure (e.g. following giving birth or surgical interventions) with the consequence of stress incontinence. The detrusor is the coarsely bundled multilayered bladder wall musculature, contraction of which leads to voiding of urine, and the sphincter is the closing muscle of the urethra. Mixed forms of these types of incontinence and so-called overflow incontinence (e.g. with benign prostate hyperplasia) or reflex incontinence (e.g. following damage to the spinal cord) occur. Further details of this complex are to be found in Chutka, D. S. and Takahashi, P. Y., 1998, Drugs 560: 587-595.

The urge to urinate is the state, aimed at voiding of urine (micturition), of increased bladder muscle tension as the bladder capacity is approached (or exceeded). This tension acts here as a stimulus to micturition. An increased urge to urinate is understood here in particular as the occurrence of premature or an increased and sometimes even painful urge to urinate up to so-called strangury. This consequently leads to a significantly more frequent micturition. Causes can be, inter alia, inflammations of the urinary bladder and neurogenic bladder disorders, and also bladder tuberculosis. However, not all the causes have yet been clarified.

An increased urge to urinate and also urinary incontinence are perceived as extremely unpleasant and there is a clear need among persons affected by these indications to achieve an improvement which is as long-term as possible.

An increased urge to urinate and in particular urinary incontinence are conventionally treated with medicaments using substances which are involved in the reflexes of the lower urinary tract (Wein, A. J., 1998, Urology 51 (Suppl. 21): 43 - 47). These are usually medicaments which have an inhibiting action on the detrusor muscle, which is responsible for the internal pressure in the bladder. These medicaments are e.g. parasympatholytics, such as oxybutynin, propiverine or tolterodine, tricyclic antidepressants, such as imipramine, or muscle relaxants, such as flavoxate. Other medicaments, which in particular increase the resistance of the urethra or of the neck of the bladder, show affinities for α-adrenoreceptors, such as

ephedrine, for β-adrenoreceptors, such as clenbutarol, or are hormones, such as oestradiol.

The review article by K.E. Andersson et al. "The pharmacological treatment of urinary incontinence", BJU International (1999), 84, 923 - 947 gives an accurate insight here into the therapeutics and treatment methods used, in particular in respect of anti-muscarine agents and other substances having a peripheral action.

Certain diarylmethylpiperazines and -piperidines are also described for this indication in WO 93/15062. For tramadol also a positive effect on bladder function has been demonstrated in a rat model of rhythmic bladder contractions (Nippon-Shinyaku, WO 98/46216). There are furthermore investigations for characterization of the opioid side effect of urinary retention in the literature, from which some indications of the influencing of bladder functions by weak opioids, such as diphenoxylate (Fowler et al., 1987 J. Urol 138:735-738) and meperidine (Doyle and Briscoe, 1976 Br J Urol 48:329-335), by mixed opioid agonists / antagonists, such as buprenorphine (Malinovsky et al., 1998 Anesth Analg 87:456-461; Drenger and Magora, 1989 Anesth Analg 69:348-353), pentazocine (Shimizu et al. (2000) Br. J. Pharmacol. 131 (3): 610 - 616) and nalbuphine (Malinovsky et al., 1998, loc. cit.), and by potent opioids, such as morphine ((Malinovsky et al., 1998 loc. cit.; Kontani and Kawabata, (1988); Jpn J Pharmacol. Sep;48(1):31) and fentanyl (Malinovsky et al., 1998 loc. cit.) result. Nevertheless, these investigations were usually carried out in analgesically active concentrations.

In the case of the indications in question here, it should be remembered that it is in general a matter of very long-term uses of medicaments and, in contrast to many situations where analgesics are employed, those affected are faced with a situation which is very unpleasant but not intolerable. It is therefore to be ensured here - even more so than with analgesics - that side effects are avoided if the person affected does not want to exchange one evil for another. Also, analgesic actions are also largely undesirable during permanent treatment of urinary incontinence.

The object of the present invention was therefore to discover substances or substance combinations which are helpful for treatment of an increased urge to urinate or urinary incontinence and, at the active doses, preferably at the same time show fewer side effects and/or analgesic actions than known from the prior art, in particular show a synergistic effect for treatment of urinary incontinence.

It has now been found, surprisingly, that a combination of compounds of group A, the opioids and other substances which have a central action and can interact with opioid receptors and the effects of which can be antagonized by naloxone, or in particular substances which act via an opiate receptor, in particular the μ-receptor, and compounds of group B, which comprises muscarine antagonists and other substances which are known to be active in urinary incontinence and have a predominantly peripheral action, have an outstanding action on bladder function. These combinations - significantly beyond that expected - furthermore already proved to be so active at very low doses that it was possible to employ the combined active

compounds in a low dose. As a result, it is to be expected that side effects which otherwise occur at the higher dosages necessary will decrease significantly, while the therapeutic action is retained in full by this combination of peripheral anti-muscarine effect acting predominantly directly on the bladder or bladder musculature and central opioid effect or μ-receptor effect.

The invention accordingly provides the use of an active compound combination of at least one of the **compounds A** and at least one of the **compounds B**, with **compound A** chosen from:

Group a) comprising:

tramadol, O-demethyltramadol, or O-demethyl-N-mono-demethyl-tramadol, as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group b) comprising:

- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine
- meptazinol

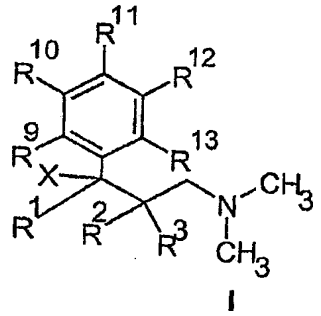
- nalbuphine
- pethidine (meperidine)
- tilidine
- tramadol
- viminol
- butorphanol
- dextromoramide
- dezocine
- diacetylmorphine (heroin)
- hydrocodone
- hydromorphone
- ketobemidone
- levomethadone
- levomethadyl acetate (l-α-acetylmethadol (LAAM))
- levorphanol
- morphine
- nalorphine
- oxycodone
- pentazocine
- piritramide
- alfentanil
- buprenorphine
- etorphine
- fentanyl
- remifentanil
- sufentanil

as the free base or acid and/or in the form of physiologically acceptable salts, in particular

in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group c) comprising:

1-phenyl-3-dimethylamino-propane compounds according to the general **formula I**



I

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^2 and R^3 in each case independently of one another are chosen from H or C_{1-4}-alkyl, branched

or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

or

R^2 and R^3 together form a saturated C_{4-7}-cycloalkyl radical, unsubstituted or mono- or polysubstituted,

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3 CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl,

branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

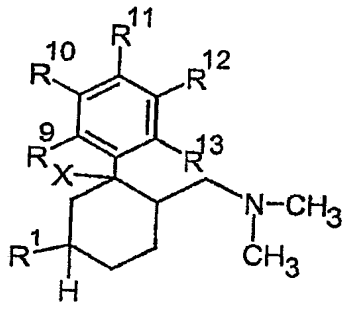
or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group d) comprising:

substituted 6-dimethylaminomethyl-1-phenylcyclohexane compounds according to the general **formula II**



II

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-alkyl, Cl or F and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$,

where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

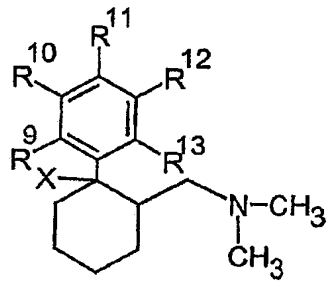
R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and/or

Group e) comprising:

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds according to the general **formula III**



III

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted, and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or

mono- or polysubstituted; $PO(O\text{-}C_{1\text{-}4}\text{-alkyl})_2$, $CO(OC_{1\text{-}5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1\text{-}3}\text{-alkyl})$, $CO(C_{1\text{-}5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1\text{-}3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is $C_{1\text{-}4}$-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; $C_{1\text{-}6}$-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

with the proviso that if R^9, R^{11} and R^{13} correspond to H and one of R^{10} or R^{12} corresponds to H and the other corresponds to OCH_3, X may not be OH,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the

enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and with at least one of the **compounds B** chosen from:

the anti-muscarine agents: atropine, oxybutinin, propiverine, propantheline, emepronium, trospium, tolterodine, darifenacin and α,α-diphenylacetic acid 4-(N-methylpiperidyl) ester, as well as duloxetine, imipramine and desmopressin,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

for the preparation of medicament for treatment of an increased urge to urinate or urinary incontinence.

Surprisingly, it has been found that the combination of the substances mentioned has a significantly positive influence on certain physiological parameters, which are of importance in cases of an increased urge to urinate or urinary incontinence. Each individual of these compounds

can mean a significant alleviation in the symptomatic picture of the patient affected.

In the context of this invention, alkyl or cycloalkyl radicals are understood as meaning saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons, which can be unsubstituted or mono- or polysubstituted. In this context, C_{1-2}-alkyl represents C1- or C2-alkyl, C_{1-3}-alkyl represents C1-, C2- or C3-alkyl, C_{1-4}-alkyl represents C1-, C2-, C3- or C4-alkyl, C_{1-5}-alkyl represents C1-, C2-, C3-, C4- or C5-alkyl, C_{1-6}-alkyl represents C1-, C2-, C3-, C4-, C5- or C6-alkyl, C_{1-7}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C_{1-8}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7- or C8-alkyl, C_{1-10}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9- or C10-alkyl and C_{1-18}-alkyl represents, C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- or C18-alkyl. Furthermore, C_{3-4}-cycloalkyl represents C3- or C4-cycloalkyl, C_{3-5}-cycloalkyl represents C3-, C4- or C5-cycloalkyl, C_{3-6}-cycloalkyl represents C3-, C4-, C5- or C6-cycloalkyl, C_{3-7}-cycloalkyl represents C3-, C4-, C5-, C6- or C7-cycloalkyl, C_{3-8}-cycloalkyl represents C3-, C4-, C5-, C6-, C7- or C8-cycloalkyl, C_{4-5}-cycloalkyl represents C4- or C5-cycloalkyl, C_{4-6}-cycloalkyl represents C4-, C5- or C6-cycloalkyl, C_{4-7}-cycloalkyl represents C4-, C5-, C6- or C7-cycloalkyl, C_{5-6}-cycloalkyl represents C5- or C6-cycloalkyl and C_{5-7}-cycloalkyl represents C5-, C6- or C7-cycloalkyl. In respect of cycloalkyl, the term also includes saturated cycloalkyls in which one or 2 carbon atoms are replaced by a heteroatom, S, N or O. However, the term cycloalkyl also includes, in particular, mono- or poly-, preferably monounsaturated cycloalkyls without a heteroatom in the

ring as long as the cycloalkyl is not an aromatic system. The alkyl and cycloalkyl radicals are preferably methyl, ethyl, vinyl (ethenyl), propyl, allyl (2-propenyl), 1-propinyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, cyclopropyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, and also adamantyl, CHF_2, CF_3 or CH_2OH, as well as pyrazolinone, oxopyrazolinone, [1,4]dioxane or dioxolane.

In connection with alkyl and cycloalkyl - as long as this is not expressly defined otherwise - the term substituted here in the context of this invention is understood as substitution of at least one (optionally also several) hydrogen radical(s) by F, Cl, Br, I, NH_2, SH or OH, where "polysubstituted" or "substituted" in the case of polysubstitution is to be understood as meaning that the substitution takes place both on different and on the same atoms several times with the same or different substituents, for example three times on the same C atom as in the case of CF_3, or at different places as in the case of $-CH(OH)-CH=CH-CHCl_2$. Particularly preferred substituents here are F, Cl and OH. In respect of cycloalkyl, the hydrogen radical can also be replaced by OC_{1-3}-alkyl or C_{1-3}-alkyl (in each case mono- or polysubstituted or unsubstituted), in particular methyl, ethyl, n-propyl, i-propyl, CF_3, methoxy or ethoxy.

The term $(CH_2)_{3-6}$ is to be understood as meaning $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH_2-$ and $-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$, $(CH_2)_{1-4}$ is to be understood as

meaning $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ and $-CH_2-CH_2-CH_2-CH_2-$, $(CH_2)_{4-5}$ is to be understood as meaning $-CH_2-CH_2-CH_2-CH_2-$ and $-CH_2-CH_2-CH_2-CH_2-CH_2-$ etc.

An aryl radical is understood as meaning ring systems with at least one armomatic ring, but without heteroatoms in even only one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl, in particular 9H-fluorenyl or anthracenyl radicals, which can be unsubstituted or mono- or polysubstituted.

A heteroaryl radical is understood as meaning heterocyclic ring systems with at least one unsaturated ring, which contain one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur and can also be mono- or polysubstituted. Examples which may be mentioned from the group of heteroaryls are furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5 thiadiazole, benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole, indole and quinazoline.

In this context, in connection with aryl and heteroaryl, substituted is understood as meaning substitution of the aryl or heteroaryl by R^{23}, OR^{23} a halogen, preferably F and/or Cl, a CF_3, a CN, an NO_2, an $NR^{24}R^{25}$, a C_{1-6}-alkyl (saturated), a C_{1-6}-alkoxy, a C_{3-8}-cycloalkoxy, a C_{3-8}-cycloalkyl or a C_{2-6}-alkylene.

In this context, the radical R^{23} represents H, a C_{1-10}-alkyl, preferably a C_{1-6}-alkyl, an aryl or heteroaryl or an aryl or heteroaryl radical bonded via a C_{1-3}-alkylene group, where

these aryl and heteroaryl radicals may not themselves be substituted by aryl or heteroaryl radicals,

the radicals R^{24} and R^{25} are identical or different and denote for H, a C_{1-10}-alkyl, preferably a C_{1-6}-alkyl, an aryl, a heteroaryl or an aryl or heteroaryl radical bonded via a C_{1-3}-alkylene group, where these aryl and heteroaryl radicals may not themselves be substituted by aryl or heteroaryl radicals,

or the radicals R^{24} and R^{25} together denote $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{26}CH_2CH_2$ or $(CH_2)_{3-6}$, and

the radical R^{26} for H, a C_{1-10}-alkyl, preferably a C_{1-6}-alkyl, an aryl or heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-3}-alkylene group, where these aryl and heteroaryl radicals may not themselves be substituted by aryl or heteroaryl radicals.

The term salt is to be understood as meaning any form of the active compound according to the invention in which this assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. This is also to be understood as meaning complexes of the active compound with other molecules and ions, in particular complexes which are complex via ionic interactions.

The term of the physiologically acceptable salt with cations or bases in the context of this invention is understood as meaning salts of at least one of the compounds according to the invention - usually a (deprotonated) acid - as the anion with at least one

preferably inorganic cation, which are physiologically acceptable - in particular when used on humans and/or mammals. Particularly preferred salts are those of the alkali metals and alkaline earth metals, but also with NH_4^+, but in particular (mono-) or (di-)sodium, (mono-) or (di-)potassium, magnesium or calcium salts.

The term of the physiologically acceptable salt with anions or acids in the context of this invention is furthermore understood as meaning salts of at least one of the compounds according to the invention - usually protonated, for example on the nitrogen - as the cation with at least one anion, which are physiologically acceptable - in particular when used on humans and/or mammals. In particular, in the context of this invention this is understood as meaning the salt formed with a physiologically acceptable acid, namely salts of the particular active compound with inorganic or organic acids which are physiologically acceptable - in particular when used on humans and/or mammals. Examples of physiologically acceptable salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro1b6-benzo[d]isothiazol-3-one (saccharic acid), monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethyl-benzoic acid, a-liponic acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid. The hydrochloride salt is particularly preferred.

Suitable salts in the context of this invention and in each use described and each of the medicaments described are salts of the particular active compound with inorganic or organic acids and/or a sugar substitute, such as saccharin, cyclamate or acesulfam. However, the hydrochloride is particularly preferred.

Compounds of **group a)** and their preparation are known from DE 44 26 245 A1. Compounds of **group b)** and **c)** and their preparation are known from DE 195 25 137 A1.

In a preferred embodiment, for the use according to the invention the **compound A** in **group a)** is chosen from:

tramadol, (+)-tramadol, (+)-O-demethyltramadol or (+)-O-demethyl-N-mono-demethyl-tramadol,
preferably tramadol or (+)-tramadol,
in particular (+)-tramadol.

In a preferred embodiment, for the use according to the invention the **compound A** in **group b)** is chosen from:

- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine
- meptazinol
- nalbuphine
- pethidine (meperidine)
- tilidine
- viminol

- butorphanol
- dezocine
- nalorphine
- pentazocine
- buprenorphine

preferably

- codeine
- dextropropxyphene
- dihydrocodeine
- meptazinol
- nalbuphine
- tilidine
- buprenorphine

In a preferred embodiment, for the use according to the invention the **compound A** in **group c)** is chosen from compounds according to **formula I** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F, $OC(O)CH_3$ or H,

and/or

R^1 is chosen from

C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably CH_3, C_2H_5, C_4H_9 or t-butyl, in particular CH_3 or C_2H_5,

and/or

R^2 and R^3 independently of one another are chosen from

H, C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably H, CH_3, C_2H_5, i-propyl or t-butyl, in particular H or CH_3, preferably R^3 = H,

or

R^2 and R^3 together form a C_{5-6}-cycloalkyl radical, saturated or unsaturated, unsubstituted or mono- or polysubstituted, preferably saturated and unsubstituted, in particular cyclohexyl.

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OCH_3 or SCH_3

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

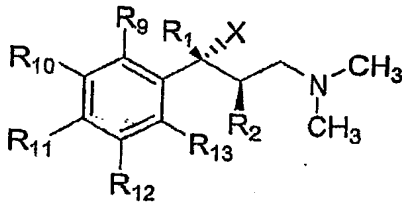
or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

In this context, it is particularly preferable for compounds of **group c)** if compounds of the **formula I** where R^3 = H are in the form of the diastereomers with the relative configuration 1a



Ia

in particular are used in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

the compounds of the **formula I** are used in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

In this context, it is particularly preferable if **compound A** chosen from the following group is used:

- (2RS,3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol
- (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,

- (3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol,
- (+)-(1R,2R)-acetic acid 3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propyl ester,
- (1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS,3RS)-3-(4-chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol and
- (+)-(2R,3R)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

preferably as the hydrochloride.

In a preferred embodiment, for the use according to the invention the **compound A** in **group d)** is chosen from compounds according to **formula II** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular OH,

and/or

R^1 is chosen from

C_{1-4}-alkyl, CF_3, OH, O-C_{1-4}-alkyl, Cl or F, preferably OH, CF_3 or CH_3,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

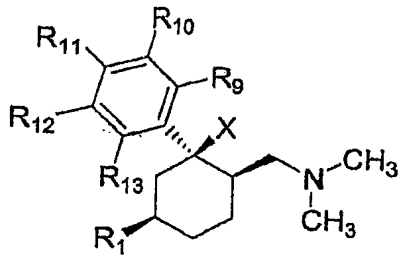
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

In this context, it is particularly preferable for compounds of **group d)** if compounds of the **formula II** are in the form of the diastereomers with the relative configuration IIa



IIa

in particular are used in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer,

and/or

the compounds of the **formula II** are used in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

In this context, it is particularly preferable if **compound A** chosen from the following group is used:

- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,

- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexane-1,3-diol,
- (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol or
- (1RS,2RS,5RS)-3-(2-dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

In a preferred embodiment, for the use according to the invention the **compound A** in **group e)** is chosen from compounds according to **formula III** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular F or H,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular characterized in that

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

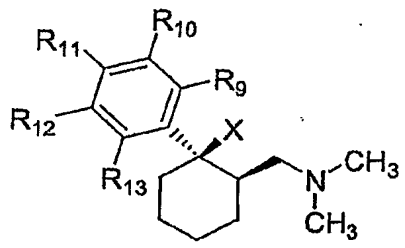
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7,

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

In this context, it is particularly preferable for compounds of **group e)** if compounds of the **formula III** are in the form of their diastereomers with the relative configuration IIIa



IIIa

in particular are used in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

the compounds of the **formula III** are used in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

In this context, it is particularly preferable if **compound A** chosen from the following group is used:

- (+)-(1R,2R)-3-(2-dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol or
- (-)-(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

For a particularly preferred use, **compound B** is chosen from:

darifenacin, duloxetine, oxybutinin or tolterodine,

preferably is chosen from

duloxetine, oxybutinin or tolterodine,

preferably is chosen from

oxybutinin or tolterodine.

Although the uses according to the invention show only a low degree of side effects, it may also be of advantage, for example to avoid certain forms of dependency, also to use morphine antagonists, in particular naloxone, naltrexone and/or levallorphan, in addition to the combination of **compounds A** and **B**.

The invention also provides an active compound combination of at least one of the **compounds A** and at least one of the **compounds B**, with **compound A** chosen from:

Group a) comprising:

tramadol, O-demethyltramadol or O-demethyl-N-mono-demethyl-tramadol, as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group b) comprising:

- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine

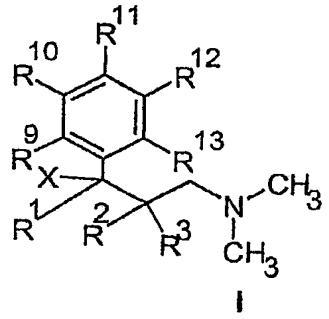
- meptazinol
- nalbuphine
- pethidine (meperidine)
- tilidine
- tramadol
- viminol
- butorphanol
- dextromoramide
- dezocine

- diacetylmorphine (heroin)
- hydrocodone
- hydromorphone
- ketobemidone
- levomethadone
- levomethadyl-acetate (l-α-acetylmethadol (LAAM))
- levorphanol
- morphine
- nalorphine
- oxycodone
- pentazocine
- piritramide
- alfentanil
- buprenorphine
- etorphine
- fentanyl
- remifentanil
- sufentanil

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group c) comprising:

1-phenyl-3-dimethylamino-propane compounds according to the general **formula I**



I

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^2 and R^3 in each case independently of one another are chosen from H or C_{1-4}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

or

R^2 and R^3 together form a saturated C_{4-7}-cycloalkyl radical, unsubstituted or mono- or polysubstituted,

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

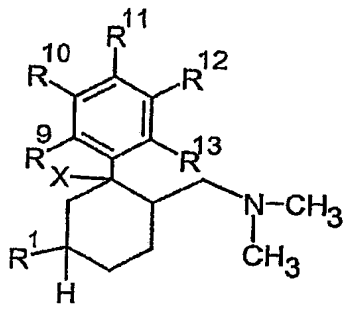
or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group d) comprising:

substituted 6-dimethylaminomethyl-1-phenylcyclohexane compounds according to the general **formula II**



II

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched,

saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-alkyl, Cl or F and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; PO(O-C_{1-4}-alkyl)$_2$, CO(OC_{1-5}-alkyl), CONH-C_6H_4-(C_{1-3}-alkyl), CO(C_{1-5}-alkyl), CO-CHR^{17}-NHR^{18}, CO-C_6H_4-R^{15}, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated,

unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

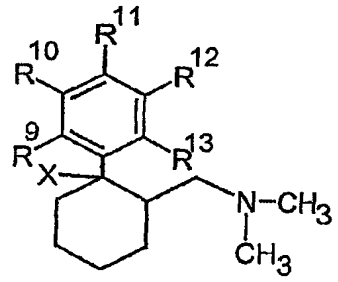
R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and/or

Group e) comprising:

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds according to the general **formula III**



III

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted, and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or

4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

with the proviso that if R^9, R^{11} and R^{13} correspond to H and one of R^{10} or R^{12} corresponds to H and the other corresponds to OCH_3, X may not be OH,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and with at least one of the **compounds B** chosen from:

the anti-muscarine agents: atropine, oxybutinin, propiverine, propantheline, emepronium, trospium, tolterodine, darifenacin and α,α-diphenylacetic acid 4-(N-methylpiperidyl) ester, as well as duloxetine, imipramine and desmopressin,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Suitable salts in the context of this invention and in each of the medicaments described are salts of the particular active compound with inorganic or organic acids and/or a sugar substitute, such as saccharin, cyclamate or acesulfam. However, the hydrochloride is particularly preferred.

For the active compound combination, it is particularly preferable if the **compound A** in **group a)** is chosen from:

tramadol, (+)-tramadol, (+)-O-demethyltramadol or (+)-O-demethyl-N-mono-demethyl-tramadol, preferably tramadol or (+)-tramadol, in particular (+)-tramadol.

For the active compound combination, it is particularly preferable if the **compound A** in **group b)** is chosen from:

- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine
- meptazinol
- nalbuphine
- pethidine (meperidine)
- tilidine
- viminol
- butorphanol
- dezocine
- nalorphine
- pentazocine
- buprenorphine

preferably

- codeine
- dextropropxyphene
- dihydrocodeine
- meptazinol
- nalbuphine
- tilidine
- buprenorphine

For the active compound combination, it is particularly preferable if the **compound A** in **group c)** is chosen from compounds according to **formula I** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F, $OC(O)CH_3$ or H,

and/or

R^1 is chosen from

C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably CH_3, C_2H_5, C_4H_9 or t-butyl, in particular CH_3 or C_2H_5,

and/or

R^2 and R^3 independently of one another are chosen from

H, C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably H, CH_3, C_2H_5, i-propyl or t-butyl, in particular H or CH_3, preferably R^3 = H,

or

R^2 and R^3 together form a C_{5-6}-cycloalkyl radical, saturated or unsaturated, unsubstituted or mono- or polysubstituted, preferably saturated and unsubstituted, in particular cyclohexyl.

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OCH_3 or SCH_3

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

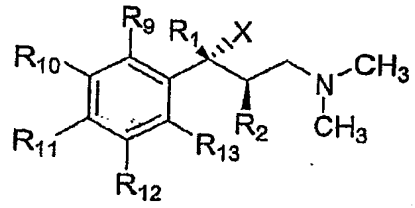
or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

In this context, it is particularly preferable for compounds of **group c)** if the compounds of the **formula I** where R^3 = H are in the form of the diastereomers with the relative configuration 1a



Ia

in particular in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

the compounds of the **formula I** are in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

In this context, it is particularly preferable if **compound A** is chosen from the following group:

- (2RS,3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol
- (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol,
- (+)-(1R,2R)-acetic acid 3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propyl ester,
- (1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS,3RS)-3-(4-chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,

- (2RS,3RS)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol and
- (+)-(2R,3R)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

preferably as the hydrochloride.

For the active compound combination, it is particularly preferable if the **compound A** in **group d)** is chosen from compounds according to **formula II** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular OH,

and/or

R^1 is chosen from

C_{1-4}-alkyl, CF_3, OH, O-C_{1-4}-alkyl, Cl or F, preferably OH, CF_3 or CH_3,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

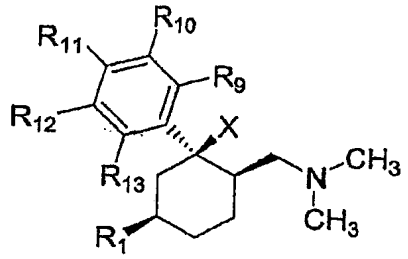
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

In this context, it is particularly preferable for compounds of **group d)** if the compounds of the **formula II** are in the form of the diastereomers with the relative configuration IIa



IIa

in particular in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer,

and/or

the compounds of the **formula I** are in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the

(-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

In this context, it is particularly preferable if **compound A** is chosen from the following group:

- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexane-1,3-diol,
- (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol or
- (1RS,2RS,5RS)-3-(2-dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

For the active compound combination, it is particularly preferable if the **compound A** in **group e)** is chosen from compounds according to **formula III** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular F or H,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular characterized in that

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

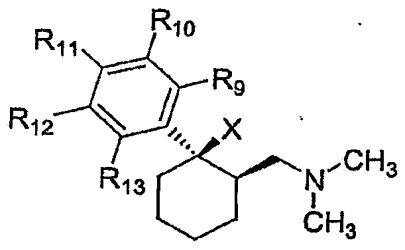
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7,

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

In this context, it is particularly preferable for compounds of **group e)** if the compounds of the **formula III** are in the form of their diastereomers with the relative configuration IIIa



IIIa

in particular in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

the compounds of the **formula III** are in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

In this context, it is particularly preferable if **compound A** is chosen from the following group:

- (+)-(1R,2R)-3-(2-dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol or
- (-)-(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

In a generally particularly preferred form of the active compound combination according to the invention the **compound B** is chosen from:

darifenacin, duloxetine, oxybutinin or tolterodine,

preferably is chosen from

duloxetine, oxybutinin or tolterodine,

preferably is chosen from

oxybutinin or tolterodine.

The invention also provides a medicament, preferably for treatment of an increased urge to urinate or urinary incontinence, comprising an active compound combination according to the invention and optionally suitable additives and/or auxiliary substances.

Suitable additives and/or auxiliary substances in the context of this invention are all the substances known to the expert from the prior art for achieving pharmaceutical formulations. The choice of these auxiliary substances and the amounts thereof to be employed depend on whether the medicament is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or locally. Formulations in the form of tablets, chewable tablets, coated tablets, capsules, granules, drops, juices or syrups are suitable for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays are suitable for parenteral, topical and inhalatory administration. Suppositories for use in the rectum are a further possibility. The use in a depot in dissolved form, a carrier film or a patch, optionally with the addition of agents which promote penetration of the skin, are examples of suitable forms for percutaneous administration. Examples of auxiliary substances and additives for the oral administration forms are disintegrating agents, lubricants, binders, fillers, mould release agents, where appropriate solvents, flavourings, sugar, in particular carrier agents,

diluents, dyestuffs, antioxidants etc. Waxes and fatty acid esters, inter alia, can be used for suppositories and carrier substances, preservatives, suspension auxiliaries etc. can be used for compositions for parenteral administration. The amounts of active compound to be administered to patients vary as a function of the weight of the patient, the mode of administration and the severity of the disease. The compounds according to the invention can be released in a delayed manner from formulation forms for oral, rectal or percutaneous use. In the indication according to the invention, appropriate sustained release formulations, in particular in the form of a "once-daily" preparation which has to be taken only once a day, are particularly preferred.

Medicaments which comprise at least 0.05 to 90.0% of the active compound, in particular dosages with a low action, in order to avoid side effects or analgesic actions, are furthermore preferred. 0.1 to 5,000 mg/kg, in particular 1 to 500 mg/kg, preferably 2 to 250 mg/kg of body weight of at least one compound of the formula I are conventionally administered. However, administration of 0.01 - 5 mg/kg, preferably 0.03 to 2 mg/kg, in particular 0.05 to 1 mg/kg of body weight, is also likewise preferred and conventional.

Auxiliary substances can be, for example: water, ethanol, 2-propanol, glycerol, ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, glucose, fructose, lactose, sucrose, dextrose, molasses, starch, modified starch, gelatines, sorbitol, inositol, mannitol, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, cellulose acetate, shellac, cetyl

alcohol, polyvinylpyrrolidone, paraffins, waxes, naturally occurring and synthetic rubbers, gum acacia, alginates, dextran, saturated and unsaturated fatty acids, stearic acid, magnesium stearate, zinc stearate, glyceryl stearate, sodium lauryl sulfate, edible oils, sesame oil, coconut oil, groundnut oil, soya bean oil, lecithin, sodium lactate, polyoxyethylene and -propylene fatty acid esters, sorbitan fatty acid esters, sorbic acid, benzoic acid, citric acid, ascorbic acid, tannic acid, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, magnesium oxide, zinc oxide, silicon dioxide, titanium oxide, titanium dioxide, magnesium sulfate, zinc sulfate, calcium sulfate, potash, calcium phosphate, dicalcium phosphate, potassium bromide, potassium iodide, talc, kaolin, pectin, crospovidone, agar and bentonite.

The medicaments and pharmaceutical compositions according to the invention are prepared with the aid of agents, devices, methods and processes which are well-known in the prior art of pharmaceutical formulation, such as are described, for example, in "Remington's Pharmaceutical Sciences", ed. A.R. Gennaro, 17th ed., Mack Publishing Company, Easton, Pa. (1985), in particular in part 8, chapter 76 to 93.

Thus e.g. for a solid formulation, such as a tablet, the active compound of the medicament can be granulated with a pharmaceutical carrier, e.g. conventional tablet constituents, such as maize starch, lactose, sucrose, sorbitol, talc, magnesium stearate, dicalcium phosphate or pharmaceutically acceptable gums, and pharmaceutical diluents, such as e.g. water, in order to form a solid composition which comprises the active compound in

homogeneous distribution. Homogeneous distribution is understood here as meaning that the active compound is distributed uniformly over the entire composition, so that this can be easily divided into unit dose forms, such as tablets, pills or capsules, with the same action. The solid composition is then divided into unit dose forms. The tablets or pills of the medicament according to the invention or of the compositions according to the invention can also be coated, or compounded in another manner, in order to provide a dose form with delayed release. Suitable coating compositions are, inter alia, polymeric acids and mixtures of polymeric acids with materials such as e.g. shellac, cetyl alcohol and/or cellulose acetate.

Although the medicaments according to the invention show only a low degree of side effects, it may be of advantage, for example to avoid certain forms of dependency, also to use morphine antagonists, in particular naloxone, naltrexone and/or levallorphan, in addition to the combination of **compounds A** and **B.**

The invention also relates to a method for treatment of an increased urge to urinate or urinary incontinence, in which the active compound combination of **compound A** and **compound B** is used.

The following examples are intended to explain the invention without the subject matter of the invention being limited thereto.

Examples

Example 1. Test system of cystometry on anaesthetized naïve rats.

The cystometric investigation on naïve female rats was carried out by the method of Kimura et al. (Kimura et al., 1996, Int. J. Urol. 3:218-227). The abdomen of anaesthetized, ventilated rats is opened up and the ureter is ligated. The urine is drained from the kidneys. A catheter is inserted into the bladder and fixed. Saline is infused into the bladder via this by means of an infusion pump, until the bladder shows rhythmic spontaneous activity in the form of contractions which can be recorded via a connected pressure transducer. After stable starting values are reached, the test substance is administered i.v. in a cumulative manner. An influence on bladder function manifests itself via suppression of the spontaneous contractions. In this context, the absence of contractions over a period of 10 min is the parameter for the suppression.

A suppression of spontaneous contractions in the rats was measurable with all the substances and combinations listed here, table 2 indicated the mean of the lowest dose of two experiments in which contractions were absent over a period of 10 min for the first time.

The substances investigated show a positive action on bladder regulation and are thus suitable for treatment of urinary incontinence.

Example 2: Parenteral administration form

20 g tramadol and 1 g tolterodine is dissolved in 1 l of water for injection purposes at room temperature and the solution is then adjusted to isotonic conditions by addition of NaCl.

Patent claims:

1. Use of an active compound combination of at least one of the **compounds A** and at least one of the **compounds B**, with **compound A** chosen from:

Group a) comprising:

tramadol, O-demethyltramadol, or O-demethyl-N-mono-demethyl-tramadol, as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group b) comprising:

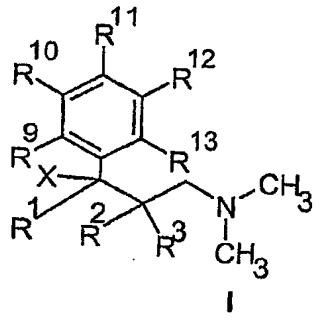
- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine
- meptazinol
- nalbuphine
- pethidine (meperidine)
- tilidine
- tramadol
- viminol
- butorphanol

- dextromoramide
- dezocine
- diacetylmorphine (heroin)
- hydrocodone
- hydromorphone
- ketobemidone
- levomethadone
- levomethadyl acetate (l-α-acetylmethadol (LAAM))
- levorphanol
- morphine
- nalorphine
- oxycodone
- pentazocine
- piritramide
- alfentanil
- buprenorphine
- etorphine
- fentanyl
- remifentanil
- sufentanil

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group c) comprising:

1-phenyl-3-dimethylamino-propane compounds according to the general **formula I**



I

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^2 and R^3 in each case independently of one another are chosen from H or C_{1-4}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

or

R^2 and R^3 together form a saturated C_{4-7}-cycloalkyl radical, unsubstituted or mono- or polysubstituted,

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3 CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

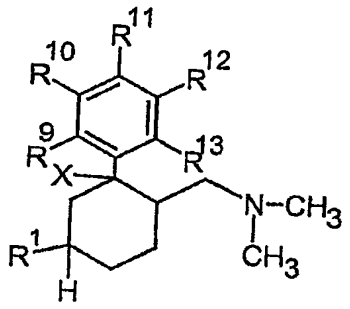
or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group d) comprising:

substituted 6-dimethylaminomethyl-1-phenylcyclohexane compounds according to the general **formula II**



II

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched

or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-alkyl, Cl or F and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or

phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

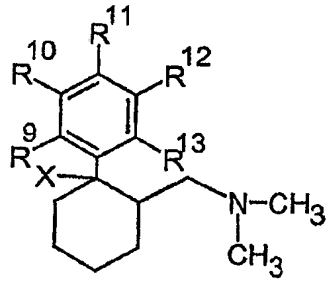
R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and/or

Group e) comprising:

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds according to the general **formula III**



III

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted, and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or

polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

with the proviso that if R^9, R^{11} and R^{13} correspond to H and one of R^{10} or R^{12} corresponds to H and the other corresponds to OCH_3, X may not be OH,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and with at least one of the **compounds B** chosen from:

the anti-muscarine agents: atropine, oxybutinin, propiverine, propantheline, emepronium, trospium, tolterodine, darifenacin and α,α-diphenylacetic acid 4-(N-methylpiperidyl) ester, as well as duloxetine, imipramine and desmopressin,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

for the preparation of a medicament for treatment of an increased urge to urinate or urinary incontinence.

2. Use according to claim 1, characterized in that the **compound A** in **group a)** is chosen from:

tramadol, (+)-tramadol, (+)-O-demethyltramadol or (+)-O-demethyl-N-mono-demethyl-tramadol, preferably tramadol or (+)-tramadol, in particular (+)-tramadol.

3. Use according to claim 1, characterized in that the **compound A** in **group b)** is chosen from:

- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine
- meptazinol
- nalbuphine

- pethidine (meperidine)
- tilidine
- viminol
- butorphanol
- dezocine
- nalorphine
- pentazocine
- buprenorphine

preferably

- codeine
- dextropropxyphene
- dihydrocodeine
- meptazinol
- nalbuphine
- tilidine
- buprenorphine

4. Use according to claim 1, characterized in that the **compound A** in **group c)** is chosen from compounds according to **formula I** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F, $OC(O)CH_3$ or H,

and/or

R^1 is chosen from

C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably CH_3, C_2H_5, C_4H_9 or t-butyl, in particular CH_3 or C_2H_5,

and/or

R^2 and R^3 independently of one another are chosen from

H, C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably H, CH_3, C_2H_5, i-propyl or t-butyl, in particular H or CH_3, preferably R^3 = H,

or

R^2 and R^3 together form a C_{5-6}-cycloalkyl radical, saturated or unsaturated, unsubstituted or mono- or polysubstituted, preferably saturated and unsubstituted, in particular cyclohexyl.

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OCH_3 or SCH_3

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

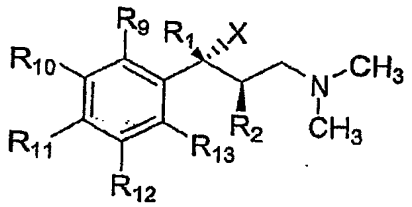
or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

5. Use according to claim 4, characterized in that compounds of the **formula I** where R^3 = H are in the form of the diastereomers with the relative configuration 1a



Ia

in particular are used in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

in that the compounds of the **formula I** are used in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

6. Use according to one of claims 4 or 5, characterized in that **compound A** chosen from the following group is used:

- (2RS,3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol
- (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,

- (3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol,
- (+)-(1R,2R)-acetic acid 3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propyl ester,
- (1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS,3RS)-3-(4-chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol and
- (+)-(2R,3R)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

preferably as the hydrochloride.

7. Use according to claim 1, characterized in that the **compound A** in **group d)** is chosen from compounds according to **formula II** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular OH,

and/or

R^1 is chosen from

C_{1-4}-alkyl, CF_3, OH, O-C_{1-4}-alkyl, Cl or F, preferably OH, CF_3 or CH_3,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

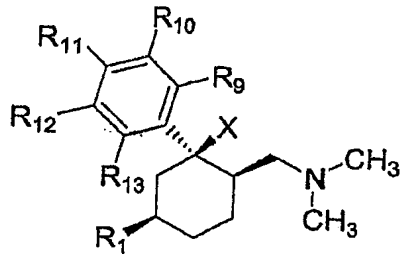
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

8. Use according to claim 7, characterized in that compounds of the **formula II** are in the form of the diastereomers with the relative configuration IIa



IIa

in particular are used in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer,

and/or

in that the compounds of the **formula II** are used in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

9. Use according to one of claims 7 or 8, characterized in that **compound A** chosen from the following group is used:

- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,

- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexane-1,3-diol,
- (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol or
- (1RS,2RS,5RS)-3-(2-dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

10. Use according to claim 1, characterized in that the **compound A** in **group e)** is chosen from compounds according to **formula III** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular F or H,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular characterized in that

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

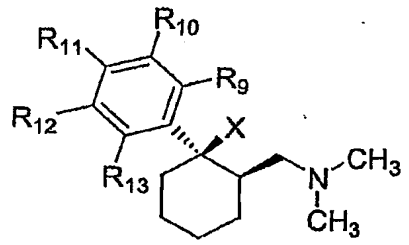
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7,

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14}, or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

11. Use according to claim 10, characterized in that compounds of the **formula III** are in the form of their diastereomers with the relative configuration IIIa



IIIa

in particular are used in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

in that the compounds of the **formula III** are used in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

12. Use according to one of claims 10 or 11, characterized in that **compound A** chosen from the following group is used:

- (+)-(1R,2R)-3-(2-dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol or
- (-)-(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

13. Use according to one of claims 1 to 12, characterized in that the **compound B** is chosen from:

darifenacin, duloxetine, oxybutinin or tolterodine,

preferably is chosen from

duloxetine, oxybutinin or tolterodine,

preferably is chosen from

oxybutinin or tolterodine.

14. Active compound combination of at least one of the **compounds A** and at least one of the **compounds B**, with **compound A** chosen from:

Group a) comprising:

tramadol, O-demethyltramadol or O-demethyl-N-mono-demethyl-tramadol, as the free base

or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group b) comprising:

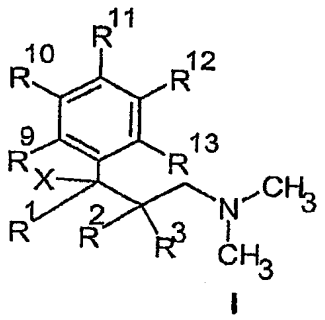
- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine
- meptazinol
- nalbuphine
- pethidine (meperidine)
- tilidine
- tramadol
- viminol
- butorphanol
- dextromoramide
- dezocine
- diacetylmorphine (heroin)
- hydrocodone
- hydromorphone
- ketobemidone
- levomethadone

- levomethadyl-acetate (l-α-acetylmethadol (LAAM))
- levorphanol
- morphine
- nalorphine
- oxycodone
- pentazocine
- piritramide
- alfentanil
- buprenorphine
- etorphine
- fentanyl
- remifentanil
- sufentanil

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group c) comprising:

1-phenyl-3-dimethylamino-propane compounds according to the general **formula I**



I

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^2 and R^3 in each case independently of one another are chosen from H or C_{1-4}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

or

R^2 and R^3 together form a saturated C_{4-7}-cycloalkyl radical, unsubstituted or mono- or polysubstituted,

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$,

$SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted,

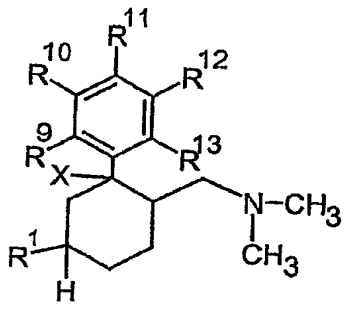
or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

Group d) comprising:

substituted 6-dimethylaminomethyl-1-phenylcyclohexane compounds according to the general **formula II**



II

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^1 is chosen from C_{1-4}-alkyl, benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-alkyl, Cl or F and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; PO(O-C_{1-4}-alkyl)$_2$, CO(OC_{1-5}-alkyl), CONH-C_6H_4-(C_{1-3}-alkyl), CO(C_{1-5}-alkyl), CO-CHR^{17}-NHR^{18}, CO-C_6H_4-R^{15}, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or

phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

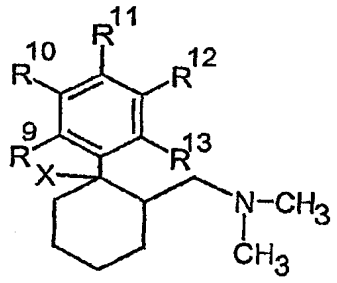
R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and/or

Group e) comprising:

6-dimethylaminomethyl-1-phenyl-cyclohexane compounds according to the general **formula III**



III

wherein

X is chosen from OH, F, Cl, H or $OC(O)R^7$, where R^7 is chosen from C_{1-3}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted, and

R^9 to R^{13} in each case independently of one another are chosen from H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, unsubstituted or mono- or polysubstituted;

where R^{14} is chosen from C_{1-6}-alkyl; pyridyl, thienyl, thiazolyl, phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted; $PO(O\text{-}C_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$, $CO(C_{1-5}\text{-alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, where R^{15} is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^{16})_2$ where R^{16} is C_{1-4}-alkyl or 4-morpholino, wherein in the radicals R^{14}, R^{15} and R^{16} the alkyl groups can be branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

where R^{17} and R18 in each case independently of one another are chosen from H; C_{1-6}-alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted; phenyl, benzyl or

phenethyl, in each case unsubstituted or mono- or polysubstituted,

or

R^9 and R^{10} or R^{10} and R^{11} together form an OCH_2O, OCH_2CH_2O, OCH=CH, CH=CHO, CH=C(CH3)O, OC(CH3)=CH, $(CH_2)_4$ or OCH=CHO ring,

with the proviso that if R^9, R^{11} and R^{13} correspond to H and one of R^{10} or R^{12} corresponds to H and the other corresponds to OCH_3, X may not be OH,

as the free base or acid and/or in the form of physiologically acceptable salts, in particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids; in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer;

and with at least one of the **compounds B** chosen from:

the anti-muscarine agents: atropine, oxybutinin, propiverine, propantheline, emepronium, trospium, tolterodine, darifenacin and α,α-diphenylacetic acid 4-(N-methylpiperidyl) ester, as well as duloxetine, imipramine and desmopressin,

as the free base or acid and/or in the form of physiologically acceptable salts, in

particular in the form of their physiologically acceptable acid and basic salts or salts with cations or bases or with anions or acids, optionally in the form of the enantiomers, diastereomers, in particular mixtures of their enantiomers or diastereomers or an individual enantiomer or diastereomer.

15. Active compound combination according to claim 14, characterized in that the **compound A** in **group a)** is chosen from:

tramadol, (+)-tramadol, (+)-O-demethyltramadol or (+)-O-demethyl-N-mono-demethyl-tramadol, preferably tramadol or (+)-tramadol, in particular (+)-tramadol.

16. Active compound combination according to claim 14, characterized in that the **compound A** in **group b)** is chosen from:

- codeine
- dextropropxyphene
- dihydrocodeine
- diphenoxylate
- ethylmorphine
- meptazinol
- nalbuphine
- pethidine (meperidine)
- tilidine
- viminol

- butorphanol
- dezocine
- nalorphine
- pentazocine
- buprenorphine

preferably

- codeine
- dextropropxyphene
- dihydrocodeine
- meptazinol
- nalbuphine
- tilidine
- buprenorphine

17. Active compound combination according to claim 14, characterized in that the **compound A** in **group c)** is chosen from compounds according to **formula I** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F, $OC(O)CH_3$ or H,

and/or

R^1 is chosen from

C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably CH_3, C_2H_5, C_4H_9 or t-butyl, in particular CH_3 or C_2H_5,

and/or

R^2 and R^3 independently of one another are chosen from

H, C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; preferably H, CH_3, C_2H_5, i-propyl or t-butyl, in particular H or CH_3, preferably R^3 = H,

or

R^2 and R^3 together form a C_{5-6}-cycloalkyl radical, saturated or unsaturated, unsubstituted or mono- or polysubstituted, preferably saturated and unsubstituted, in particular cyclohexyl.

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OCH_3 or SCH_3

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

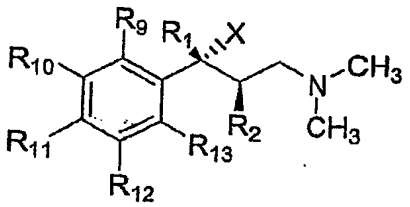
or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

18. Active compound combination according to claim 17, characterized in that the compounds of the **formula I** where R^3 = H are in the form of the diastereomers with the relative configuration 1a



Ia

in particular in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

in that the compounds of the **formula I** are in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

19. Active compound combination according to one of claims 17 or 18, characterized in that the **compound A** is chosen from the following group:

- (2RS,3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol
- (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,

- (3RS)-1-dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol,
- (+)-(1R,2R)-acetic acid 3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propyl ester,
- (1RS)-1-(1-dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS,3RS)-3-(4-chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol and
- (+)-(2R,3R)-4-dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

preferably as the hydrochloride.

20. Active compound combination according to claim 14, characterized in that the **compound A** in **group d)** is chosen from compounds according to **formula II** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular OH,

and/or

R^1 is chosen from

C_{1-4}-alkyl, CF_3, OH, O-C_{1-4}-alkyl, Cl or F, preferably OH, CF_3 or CH_3,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

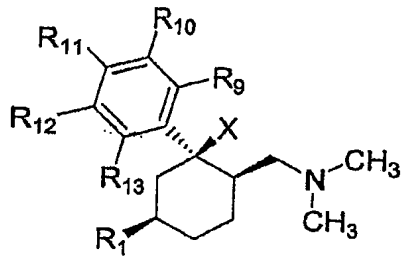
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7.

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

21. Active compound combination according to claim 20, characterized in that the compounds of the **formula II** are in the form of the diastereomers with the relative configuration IIa



IIa

in particular in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer,

and/or

in that the compounds of the **formula I** are in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

22. Active compound combination according to one of claims 20 or 21, characterized in that **compound A** is chosen from the following group:

- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,

- (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexane-1,3-diol,
- (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol or
- (1RS,2RS,5RS)-3-(2-dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

23. Active compound combination according to claim 14, characterized in that the **compound A** in **group e)** is chosen from compounds according to **formula III** for which:

X is chosen from

OH, F, Cl, $OC(O)CH_3$ or H, preferably OH, F or H, in particular F or H,

and/or

R^9 to R^{13}, where 3 or 4 of the radicals R^9 to R^{13} must correspond to H, independently of one another are chosen from

H, Cl, F, OH, CF_2H, CF_3 or C_{1-4}-alkyl, saturated and unsubstituted, branched or unbranched; OR^{14} or SR^{14}, where R^{14} is chosen from C_{1-3}-alkyl, saturated and unsubstituted, branched or unbranched;

preferably H, Cl, F, OH, CF_2H, CF_3, OCH_3 or SCH_3

or R^{12} and R^{11} form a 3,4-OCH=CH ring

in particular characterized in that

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, CF_2H, CF_3, OR^{14} or SR^{14}, preferably OH, CF_2H, OR^{14} or SCH_3, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3,

or

if R^9 and R^{13} correspond to H and R^{11} corresponds to OH, OCH_3, Cl or F, preferably Cl, one of R^{10} or R^{12} also corresponds to H while the other corresponds to OH, OCH_3, Cl or F, preferably Cl,

or

if R^9, R^{10}, R^{12} and R^{13} correspond to H, R^{11} is chosen from CF_3, CF_2H, Cl or F, preferably F,

or

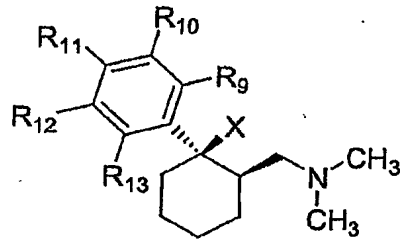
if R^{10}, R^{11} and R^{12} correspond to H, one of R^9 or R^{13} also corresponds to H while the other is chosen from OH, OC_2H_5 or OC_3H_7,

very particularly preferably

if R^9, R^{11} and R^{13} correspond to H, one of R^{10} or R^{12} also corresponds to H while the other is chosen from:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14}, or SR^{14}, preferably OH or OR^{14}, in particular OH or OC_{1-3}-alkyl, preferably OH or OCH_3.

24. Active compound combination according to claim 23, characterized in that the compounds of the **formula III** are in the form of their diastereomers with the relative configuration IIIa



IIIa

in particular in mixtures with a higher content of this diastereomer compared with the other diastereomer or as the pure diastereomer

and/or

in that the compounds of the **formula III** are in the form of the (+)-enantiomer, in particular in mixtures with a higher content of the (+)-enantiomer compared with the (-)-enantiomer of a racemic compound or as the pure (+)-enantiomer.

25. Active compound combination according to one of claims 23 or 24, characterized in that the **compound A** is chosen from the following group:

- (+)-(1R,2R)-3-(2-dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol or
- (-)-(1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol,

preferably as the hydrochloride.

26. Active compound combination according to one of claims 14 to 25, characterized in that the **compound B** is chosen from:

darifenacin, duloxetine, oxybutinin or tolterodine,

preferably is chosen from

duloxetine, oxybutinin or tolterodine,

preferably is chosen from

oxybutinin or tolterodine.

27. Medicament, preferably for treatment of an increased urge to urinate or urinary incontinence, comprising an active compound combination according to one of claims 14 to 26 and optionally suitable additives and/or auxiliary substances.

Abstract

The invention relates to the use of a combination of compounds of group A, in particular opioids, and compounds of group B, in particular anti-muscarine agents and other substances which have a predominantly peripheral action, for the preparation of a medicament for treatment of an increased urge to urinate or urinary incontinence and to corresponding medicaments and methods for treatment of an increased urge to urinate or urinary incontinence.